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Original article

Long-term effects of irbesartan on plasma aldosterone concentration and left atrial volume in hypertensive patients

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ABSTRACT

Background: Plasma aldosterone concentration (PAC) is related to cardiac remodeling in patients with hypertension. However, we do not know the detailed relationship between changes in PAC and regression of left atrial (LA) volume following long-term treatment with angiotensin II receptor blocker (ARB) or calcium-channel blocker (CCB).
Objective: The aim of this study was to investigate the effects of anti-hypertensive monotherapy, an ARB irbesartan or a CCB amlodipine, on PAC and LA reverse remodeling in hypertensive patients.
Methods: A total of 48 patients with untreated hypertension were randomly assigned to irbesartan (ARB group, $n = 26$) and amlodipine (CCB group, $n = 22$). We examined the correlation between LA volume index (LAVI) and other echocardiographic parameters or PAC ($n = 40$) at the baseline and after 12 months of treatment.
Results: After 12 months, blood pressure (BP) decreased similarly in both groups. LAVI and PAC significantly decreased in the ARB group, but not in the CCB group ($-16 \pm 8\%$ vs. $22 \pm 9\%$, $p < 0.01$, $-16 \pm 9\%$ vs. $11 \pm 9\%$, $p < 0.05$). Larger %-decrease in PAC was associated with larger %-reduction of LAVI in the ARB group ($r = 0.54$, $p < 0.05$), but not in the CCB group.
Conclusions: While BP reduction was similar between the two groups, decrease in LA volume was larger in the ARB group than in the CCB group. Decrease in LA volume was larger in patients with a greater decrease in PAC than in those with smaller decrease in PAC. ARB may facilitate reverse remodeling of LA through decreases in PAC in hypertensive patients.

Introduction

Hypertension leads to adverse cardiac remodeling, such as left atrial (LA) enlargement, left ventricular (LV) hypertrophy, and cardiac fibrosis [1,2]. Cardiac remodeling is associated with increased morbidity and mortality due to subsequent heart failure [3]. Clinical studies have shown that inhibiting the renin–aldosterone system using angiotensin-converting enzyme (ACE) inhibitors or angiotensin type II receptor blockers (ARB) induced cardiac reverse remodeling [4–6]. Moreover, plasma aldosterone has a crucial role in development of cardiac remodeling [7]. We previously reported that the inhibition of plasma aldosterone works as a contributor to regression of LV mass in hypertensive patients following long-term treatment with ARB or calcium channel blocker (CCB) [8].

LA enlargement [9–13] is strongly correlated with atrial fibrillation and mortality in hypertensive patients. Further, LA reverse remodeling by the ARB losartan was reported to be associated with absence of new onset of atrial fibrillation [5]. However, it is unclear whether ARB or CCB could decrease plasma aldosterone concentration (PAC) and LA volume in patients with untreated hypertension. Thus, the aim of this study was to investigate the impact of decrease

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in PAC as a contributor to regression of LA volume index in hypertensive patients following long-term treatment with ARB or CCB.

Materials and methods

Subjects

We enrolled 48 patients with untreated hypertension who presented to the outpatient clinic of Hyogo College of Medicine between January 2010 and December 2012. Patients were included in the study if they met the following criteria: 20 years of age or older, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 140 and 90 mmHg or over. Patients were excluded if they had secondary hypertension of any cause, angina pectoris or acute coronary artery disease, current or recent history of congestive heart failure, valvular heart diseases, cardiac arrhythmias, renal dysfunction (serum creatinine level over 2.0 mg/dl), or diabetes mellitus. Informed consent was obtained from all patients, and the study was designed to comply with the ethical principles of our institution. Eligible patients were randomly assigned in a 1:1 ratio to receive either amlodipine 2.5 mg daily (CCB group) or irbesartan 100 mg daily (ARB group). Target SBP and DBP were below 140 and 90 mmHg, respectively. If blood pressure reduction did not achieve the target level after 4 weeks, the dose of amlodipine was doubled to 5 mg, and irbesartan to 200 mg. The third and fourth steps of treatment included the addition of a thiazide and/or alpha-blocker.

Blood chemistry

Among 48 subjects, we could collect blood samples for PAC and B-type natriuretic peptide (BNP) measurement from 20 patients each in the ARB and CCB groups. Blood samples ($n = 40$) were taken between 09.00 and 11.00 h and were immediately placed on ice and centrifuged within 1 h. The specimens were stored at −80 °C until analysis. PAC was measured with a radioimmunoassay kit (SPAC-S Aldosterone Kit; Otsuka Pharmaceutical Co., Ltd., TFB, Tokyo, Japan). Plasma BNP concentration was measured with a Shionoria BNP kit (Shionogi Inc., Tokyo, Japan).

Echocardiographic studies

Transthoracic echocardiography was performed at baseline and 12 months after treatment in all patients. Echocardiography was recorded with iE33 (Philips Medical Systems, Bothell, WA, USA). A standard, comprehensive, M-mode, 2-dimensional echocardiography and Doppler study were conducted according to the guideline of the American Society of Echocardiography [14]. LA volume was calculated with a formula using an ellipsoid model and was indexed to the body surface area, i.e. LAVI [15]. LV mass index (LVMI) and relative wall thickness (RWT) were measured by the method described previously [8]. Peak velocities of early diastolic phase (E) and late diastolic phase (A) of mitral inflow, and the E/A ratio were measured by pulsed-wave Doppler echocardiography with the sample volume between mitral leaflet tips. Mitral annulus velocities (E') and E/E' ratio were measured at the septal annulus by tissue Doppler imaging.

Ethics

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki after receiving approval from the institutional review board of Hyogo College of Medicine. All subjects provided written informed consent prior to participation.

Statistical analysis

The primary outcomes included changes in PAC and LA volume in hypertensive patients following long-term treatment with amlodipine or irbesartan. Continuous data are presented as mean (±SD). We compared values at baseline and after treatment using paired t-test. The correlations between LAVI and PAC, LVMI and E/E' were examined using linear regression analysis. A p-value less than 0.05 was considered significant. Statistical computations were performed with JMP version 10.0.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics

There were 35 men and 13 women with a mean age of 62 years. The final dose of amlodipine was 145 ± 57 mg/day and that of irbesartan was 4.4 ± 1.2 mg/day. Thiazide indapamide 1 mg was added to the basal medications in two patients in the ARB group and three patients in the CCB group and the alpha blocker doxazosin 1 mg was added to three patients in the CCB group and no patients in the ARB group. Baseline characteristics were similar in both groups of patients (Table 1).

Changes in blood pressure and echocardiographic parameters and humoral factors

After 12 months of treatment, SBP, DBP, and LVMI decreased similarly in both ARB and CCB groups. Heart rate (HR), E/A, deceleration time (DT) of E wave and natural logarithm of brain natriuretic peptide (Ln BNP) did not change in either group. The LA dimension (LAD) tended to decrease in the ARB group, and tended to increase in the CCB group. The LAVI, E/E', and PAC significantly decreased in the ARB group, but not in the CCB group. The E and A were significantly increased in the CCB group, but not in the ARB group (Table 2).

Table 1
Baseline characteristics of study subjects.

	ARB ($n = 26$)	CCB ($n = 22$)	p-Value
Age (years)	63 ± 12	60 ± 13	0.68
Sex (female/male)	7F, 19M	6F, 16M	0.32
BMI	24 ± 3	24 ± 4	0.17
SBP (mmHg)	161 ± 20	162 ± 19	0.29
DBP (mmHg)	92 ± 15	94 ± 12	0.60
HR (bpm)	69 ± 12	66 ± 17	0.52
LAD (mm)	36 ± 6	36 ± 5	0.92
LAVI (ml/m^2)	24 ± 7	22 ± 6	0.26
LVEDD (mm)	48 ± 5	49 ± 4	0.60
LVESD (mm)	30 ± 5	29 ± 7	0.47
RWT	0.40 ± 0.06	0.41 ± 0.01	0.51
LVEF (%)	67 ± 7	67 ± 5	0.45
LVMI (g/m^2)	96 ± 26	102 ± 16	0.45
Comorbidity			
Dyslipidemia (%)	8 (31)	10 (45)	0.29
Smoking (%)	2 (7)	1 (5)	0.65
Baseline medication			
Statin n (%)	4 (15)	7 (32)	0.94

ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LAD, left atrial diameter; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

Table 2
Changes in hemodynamic and echocardiographic parameters, and hormone levels in ARB and CCB groups.

	ARB ($n=26$)		CCB ($n=22$)	
	Before treatment	12 months	Before treatment	12 months
Age (years)	63 ± 12		60 ± 13	
Sex (female/male)	7F, 19M		6F, 16M	
BMI	24 ± 3	24 ± 3	24 ± 4	24 ± 4
SBP (mmHg)	161 ± 20	129 ± 16**	162 ± 19	132 ± 14**
DBP (mmHg)	92 ± 15	77 ± 14**	94 ± 12	81 ± 10**
HR (bpm)	69 ± 12	69 ± 13	66 ± 17	73 ± 11
PAC (pg/dl)	126 ± 64	101 ± 59*	124 ± 51	134 ± 69
Ln BNP (pg/ml)	3.0 ± 1.1	2.8 ± 0.9	2.8 ± 1.0	2.6 ± 1.0
LAD (mm)	36 ± 6	35 ± 5	36 ± 5	37 ± 4
LAVI (ml/m^2)	24 ± 7	20 ± 6**	22 ± 6	24 ± 6
LVEDD (mm)	48 ± 5	47 ± 4**	48 ± 4	49 ± 4
LVESD (mm)	30 ± 5	29 ± 4	29 ± 7	30 ± 4
RWT	0.40 ± 0.06	0.37 ± 0.04*	0.41 ± 0.01	0.38 ± 0.05*
LVEF (%)	67 ± 7	67 ± 5	67 ± 5	67 ± 6
LVMI (g/m^2)	96 ± 26	78 ± 12**	102 ± 16	91 ± 15**
E (m/s)	63 ± 11	58 ± 14	56 ± 13	68 ± 15**
A (m/s)	77 ± 17	73 ± 16	70 ± 19	79 ± 20**
E/*A*	0.80 ± 0.14	0.81 ± 0.21	0.85 ± 0.31	0.91 ± 0.27
DT (ms)	215 ± 52	195 ± 39	205 ± 46	203 ± 53
E′ (cm/s)	5.6 ± 1.5	6.6 ± 1.7***	5.7 ± 1.6	6.0 ± 1.7
E/*E*′	11 ± 5	9 ± 3*	11 ± 3	12 ± 3

ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PAC, plasma aldosterone concentration; Ln BNP, natural logarithm brain natriuretic peptide; LAD, left atrial diameter; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; DT, deceleration time.
* $p<0.05$ vs. baseline.
** $p<0.01$ vs. baseline.
*** $p<0.001$ vs. baseline.

Effects of ARB and CCB on LAVI, LVMI, and PAC

Percent changes from the baseline in LAVI, LVMI, and PAC were significantly different between the ARB and CCB groups (−16 ± 8% vs. 22 ± 9%, $p<0.01$, −9 ± 2% vs. −16 ± 2%, $p<0.05$, −16 ± 9% vs. 11 ± 9%, $p<0.05$, respectively) (Figs. 1–3).

Correlations between LAVI and PAC, and LVMI and E/E′

Percent change in PAC was correlated with percent change in LAVI in the ARB group ($r=0.54$, $p<0.05$), but not in the CCB group (Fig. 4). Percent change in LVMI was correlated with that in LAVI in the ARB group ($r=0.46$, $p<0.05$), but not in the CCB group (Fig. 5). Percent change in *E*/*E*′ was correlated with that in LAVI in the ARB group ($r=0.53$, $p<0.01$) and in the CCB group as well ($r=0.48$, $p<0.05$, Fig. 6). Percent change in SBP was not correlated with percent change in LAVI either in the ARB group or the CCB group.

Discussion

The main findings in the present study were: (1) while blood pressure reduction over 12 months was similar between the ARB and CCB groups, PAC, *E*/*E*′, and LAVI decreased only in the ARB group; and (2) in the ARB group, percent decrease in LAVI was correlated with percent decrease in PAC.

These data suggest that ARB decreased LV filling pressure and LA volume through reduction of PAC in hypertensive patients.

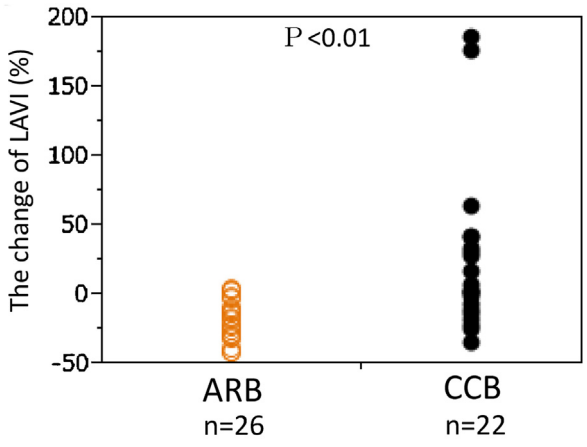

Fig. 1. Percent changes in left atrial volume index (LAVI). LAVI decreased in the ARB group but not in the CCB group after 12 months of treatment. $p<0.05$. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

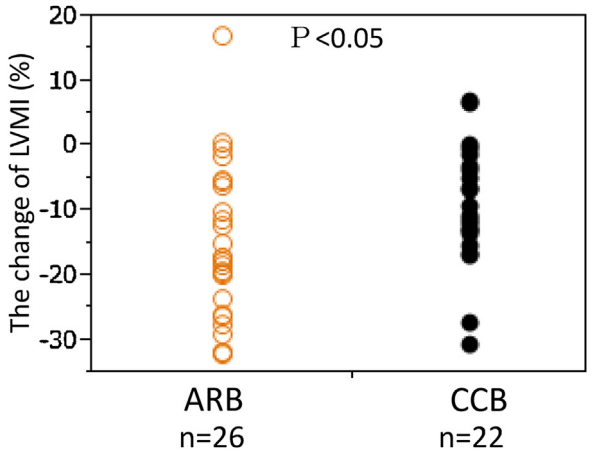

Fig. 2. Percent changes in left ventricular mass index (LVMI). Percent decrease in LVMI was greater in the ARB group than that in the CCB group. $p<0.05$. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

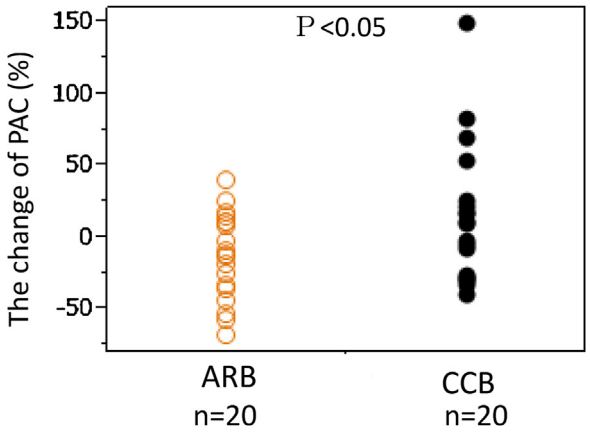

Fig. 3. Percent change in plasma aldosterone concentration (PAC). PAC decreased in the ARB group but not in the CCB group after 12 months of treatment. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

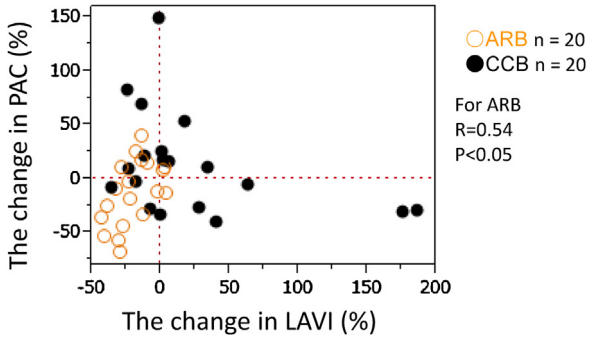

Fig. 4. Correlation between percent change in left atrial volume index (LAVI) and percent change in plasma aldosterone concentration (PAC). Larger percent decrease in PAC was associated with larger percent reduction in LAVI in the ARB group but not in the CCB group. Open circles stand for the data of the ARB group, and closed circles are those of the CCB group. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

Effect of irbesartan on hemodynamics, left ventricular mass, and left atrial volume

In our study, the reduction in systolic and diastolic blood pressure after 12-month treatment was not significantly different between the ARB and CCB groups. Body weight and heart rate did not change throughout the study period. Nonetheless, LV mass

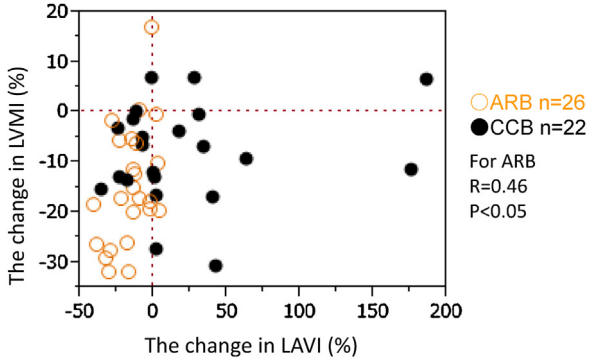

Fig. 5. Correlation between percent change in left atrial volume index (LAVI) and percent change in left ventricular mass index (LVMI). Larger percent decrease in LVMI was associated with larger percent reduction in LAVI in the ARB group than in the CCB group. Open circles stand for the data for the ARB group, and closed circles are those for the CCB group. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

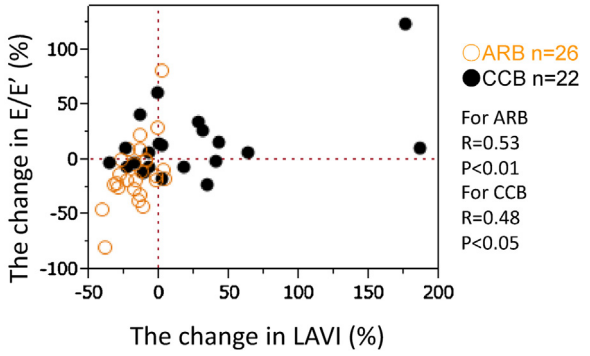

Fig. 6. Correlation between percent change in left atrial volume index (LAVI) and percent change in ratio of transmitral *E* wave peak velocity to average mitral annular *E*′ velocity (*E*/*E*′). Larger percent decrease in *E*/*E*′ was associated with larger percent reduction of LAVI in ARB group. Larger percent increase in *E*/*E*′ was associated with larger percent increase in LAVI in the CCB group. Open circles stand for the data of the ARB group, and closed circles are those of the CCB group. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

decreased more in the ARB group than in the CCB group ($-9 \pm 2\%$ vs. $-16 \pm 2\%$, $p < 0.05$, Fig. 2). LAD and LAVI decreased only in the ARB group, not in the CCB group (Table 2 and Fig. 1). In other words, the magnitude of decrease not only in LA volume, but also in *E*/*E*′ and LVMI was larger in the ARB group than in the CCB group. These data suggest that the ARB irbesartan may have a beneficial effect on LV filling pressure and LA volume as well.

Role of left atrial structural remodeling for cardiac events

Enlargement of LA has adverse cardiovascular outcomes, including stroke [9], heart failure [16–18], atrial fibrillation [19], and mortality [20]. LA enlargement has been strongly associated with LV diastolic dysfunction, independent of LV ejection fraction, age, gender, and cardiovascular risk score [21,22]. Since LA enlargement can be attributed to a sustained elevation of LV filling pressure and an atrial volume overload due to diastolic dysfunction in hypertensive patients [23,24], the LA volume reduction might be associated with improvement in cardiovascular events. However, it has not been fully clarified whether the LA volume reduction directly results in the improvement in cardiovascular outcomes.

Effect of irbesartan on PAC and LA reverse remodeling

In the ARB group of the present study, the larger decrease in PAC was associated with the larger reduction of LAVI. Elevated plasma aldosterone levels promote hypertension, cardiac fibrosis, left ventricular hypertrophy, and endothelial dysfunction [8,25]. Conversely, blockade of the renin–angiotensin–aldosterone system can result in favorable effects on cardiac remodeling. In the LIFE trial, the ARB losartan reduced LA diameter index in hypertensive patients with LV hypertrophy. In the SILVHIA study, irbesartan improved myocardial fibrosis and diastolic dysfunction in patients with hypertension with LV hypertrophy [26,27]. Moreover, irbesartan has an anti-inflammatory effect and an anti-oxidative effect, in addition to its antihypertensive effect [28–30]. Inhibition of the renin–angiotensin–aldosterone system by ARB or ACE inhibitors was reported to improve LA fibrotic change, which is found in atrial tissue of hypertensive patients [31,32]. Further, no correlation was seen between percent change in SBP and percent change in LAVI either in the ARB group or in the CCB group. Thus, LA reverse remodeling may be attributed to the reduction in LA afterload and/or to the decrease in PAC due to ARB, which in turn would improve

diastolic dysfunction through reduction of LVMI and LV filling pressure.

Effect of amlodipine on PAC and LA volume

The L-type CCB, amlodipine, might activate the renin–angiotensin–aldosterone system by an increase in sympathetic tone via a rapid and large reduction in blood pressure [33–35]. Nishimura et al. described increment in LV end-diastolic pressure as well as prolongation of the time constant of relaxation by CCB [36]. Chen et al. showed that hypertensive patients on CCB therapy seemed to have larger size of LAVI compared with patients on ACE inhibitors or ARBs [37]. Amlodipine has been reported to increase the prevalence of congestive heart failure more than irbesartan [38].

In our study, LA volume was not changed by amlodipine treatment, with an effective percent change of 22% over 12 months. Moreover, there was no difference in E/E' and PAC between the baseline and follow-up in the CCB group, in which a sustained high level of PAC may lead to elevation of LV filling pressure and LA pressure. Amlodipine may not supress LA remodeling because of lesser magnitude of LVMI reduction or sustained high level of PAC. Two patients in the CCB group showed over 150% increase in LAVI. Although both patients had modest increase in body mass index from 24 to 25 kg/m^2, their homeostasis model assessment ratio (HOMA-R) markedly rose from 3.4 to 8.4 and 1.2 to 4.5 during the study period. Development in insulin resistance might be associated with LAVI increase. We need more patients to confirm the exact mechanisms of increment in LAVI.

The present study showed that more reduction in PAC was provided with irbesartan than with amlodipine, and this might reduce LV hypertrophy, LA volume, and LV filling pressure. LA size reduction by the ARBs, losartan or valsartan was associated with absence of new onset of atrial fibrillation in patients with hypertension [5,39–41]. Irbesartan decreased LV filling pressure and LV hypertrophy much more than amlodipine despite similar blood pressure lowering, which might reduce the risk of future atrial fibrillation in patients with hypertension.

Limitations

Several limitations are included in this study. First, this is a single-center study conducted only in Japan and the number of enrolled patients is limited. Therefore, a large multicenter study is needed to confirm our results. Second, we used only one drug for each patient group (irbesartan and amlodipine). Although they are common medications for treatment of hypertension in our institute, comparison with other ARBs and CCBs may be needed in the future. Third, neither hemodynamic data (such as LV or atrial pressure) nor myocardial biopsy for estimation of fibrosis was available in the present study. In future, we need to elaborate the detailed relations between cardiac hemodynamics, myocardial tissue pathology, and left atrial structure.

Fourth, we only measured a single point of daytime BP, and nocturnal BP might be different in the ARB and CCB groups. Therefore 24-h ambulatory BP monitoring may be necessary in future studies.

Conclusions

The ARB irbesartan seems to decrease PAC, LVMI, and LAVI, differently from the CCB amlodipine. There were significant correlations between percent decrease in PAC and percent decreases in LVMI and LAVI. These data suggest that suppression of PAC by irbesartan contributed to reverse remodeling of LA and LV in hypertensive patients.

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